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(54) Quarternary Derivatives of Noroxymorphone which Relieve  
Nausea and Vomiting

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(30) (US) U.S.A. 092,470 1987/09/03

(57) 19 Claims

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QUATERNARY DERIVATIVES OF NORKYMORPHONE  
WHICH RELIEVE NAUSEA AND EMESIS

5 The administration of therapeutic doses of morphine and other clinically useful narcotic analgesics is often accompanied by unpleasant side effects on the gastro-intestinal system. For instance, morphine and related opiates such as meperidine and methadone may retard  
10 intestinal mobility by causing contractions of the small bowel circular smooth muscle.

Morphine and related narcotics may also induce nausea and increased mobility of the gastro-intestinal tract  
15 resulting in nausea or vomiting. These side effects are caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. (Goodman and Gilman, The Pharmacological Basis of Therapeutics, p. 502 (6th ed. 19001). Studies have shown that morphine and other  
20 narcotics cause emesis in dogs. For example, Wang and Glaviano, JNET 111:329-334 (9143), reported that administration of 0.5 mg/kg of morphine intravenously to 12 dogs resulted in emesis in 9 dogs within an average of 2.4 minutes. (Mg/kg refers to milligrams of morphine per  
25 kilograms of body weight.) When 1.0 mg/kg of

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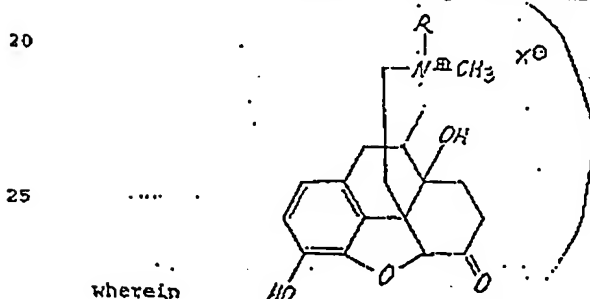
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1 morphine was administered intramuscularly to 13 dogs, 12  
of them vomited within an average time of 3.5 minutes.

5 U. S. Patent No. 4,176,186 to myself and others  
disclosed treatment of intestinal immobility associated  
with the use of narcotic analgesics through the  
administration of quaternary derivatives of  
10 norexymorphone. It has now been discovered that the  
same compounds are also useful for the treatment, both  
prophylactic and therapeutic, of the nausea and vomiting  
associated with the administration of these drugs.

15 According to the invention, therefore, nausea and  
vomiting by warm-blooded animals receiving morphine and  
related opiates, meperidine, methadone or the like, may  
be prevented or relieved by the administration of  
methylnaltrexone or other quaternary derivatives of  
norexymorphone represented by the formula:



wherein

30 R is allyl or a related radical such as  
chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride,  
bromide, iodide or methylsulfate anion.

35 These compounds are administered to the animal  
either prior to or simultaneously with the  
administration of the narcotic analgesic. They may be

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administered either enterally or parenterally. There has not been observed any interference with the analgesic activity of the opiate.

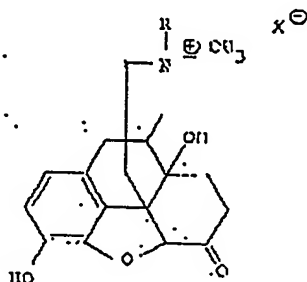
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As used herein, unless the sense of the usage indicates otherwise, the term "morphine" refers to any narcotic analgesic.

10

This invention relates to the use of quaternary derivatives of noroxymorphone to prevent or relieve nausea and vomiting associated with the administration of morphine to warm-blooded animals. The useful compounds are represented by the formula:

15



20

25

wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

30

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

35

The compounds are synthesized as described in United States Patent No. 4,176,186. A particularly preferred noroxymorphone derivative is methylnaltrexone, but other compounds represented by the above formula are also suitable.

Methylnaltrexone or other noroxymorphone derivatives may be administered to the patient either

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enterally or parenterally. However, a preferred method of administration is by injection. Nausea and emesis may follow after even a single dose of morphine, unlike intestinal immobility which is usually the effect of chronic repeated usage of the drug. Consequently, it is contemplated that the patient will be given an injection of methylnaltrexone prior to surgery or other occasion when morphine is used to treat acute pain.

As illustrated by the following Controls and Examples, our studies show that methylnaltrexone inhibits emesis when administered either together with the morphine or before the morphine is administered. It is thought that methylnaltrexone or other quaternary noroxymorphone derivatives may be administered up to two hours before the administration of morphine, but that period may be variable. In our studies, methylnaltrexone was administered intramuscularly by means of a syringe. Methylnaltrexone may also be administered enterally or parenterally by other means. It has been found to be effective in dosages in the range of about 0.05 mg/kg to about 1.0 mg/kg for each 1 mg/kg of administered morphine. It was found effective when administered in the same syringe as morphine and also when administered up to about one hour before the administration of morphine.

The effect of methylnaltrexone in reversing the emetic effects of morphine is illustrated herein. The unit of mg/kg refers to milligrams of substance administered per kilograms of body weight.

#### CONTROL 1 AND EXAMPLE 1

One mg/kg of morphine was administered intramuscularly to five dogs. Four dogs vomited. In each instance, vomiting occurred within four minutes. On a different day the same dose of morphine was

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1 administered intramuscularly to the same five dogs in  
the same syringe with 1 mg/kg of methylnaltrexone. None  
of the dogs vomited.

5 CONTROL 2 AND EXAMPLE 2

Six dogs were given intramuscular doses of 1 mg/kg  
of morphine. All six dogs vomited. On an additional  
day the same dose of morphine was combined with 0.5  
mg/kg of methylnaltrexone and administered in the same  
10 syringe to the same dogs. None of the dogs vomited.

CONTROL 3 AND EXAMPLE 3

One mg/kg of morphine was administered  
intramuscularly to three dogs. All three dogs vomited.  
15 On an additional day the morphine was combined with 0.25  
mg/kg of methylnaltrexone and administered in the same  
syringe. None of the dogs vomited.

CONTROL 4 AND EXAMPLE 4

20 Methylnaltrexone was administered to two dogs prior  
to the administration of 1 mg/kg morphine. In one dog,  
0.5 mg/kg of methylnaltrexone was administered  
intramuscularly 15 minutes before the morphine. No  
vomiting occurred. In the second dog, the same dose of  
25 methylnaltrexone was administered 30 minutes before the  
administration of morphine. No vomiting occurred.

CONTROL 5 AND EXAMPLE 5

0.05 mg/kg methylnaltrexone was administered  
30 intravenously to four dogs one minute prior to the  
administration of 1.0 mg/kg morphine. No vomiting  
occurred in any of the dogs. On a different day, the  
same animals were given 1.0 mg/kg morphine without the  
administration of methylnaltrexone. All four dogs  
35 vomited.

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The administration of methylnaltrexone alone was found to produce no noticeable effects in the animals. Previous studies with larger doses of methylnaltrexone have

- 5 demonstrated that unlike the non-quaternary naltrexone, methylnaltrexone does not precipitate withdrawal systems in morphine-tolerant dogs. Russell et al., Eur. J. Pharmacol. 78:255-261 (1982). Methylnaltrexone has not been found to interfere with the analgesic activity of morphine or
- 10 narcotic.

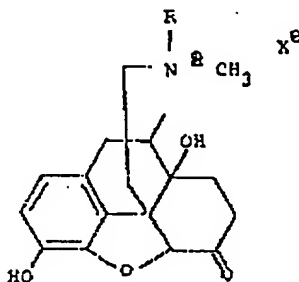
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C.



R is allyl or a related radical; and  
X is the anion of an acid;

2. Use as claimed in claim 1 in which R is chloroalkyl, cyclopropyl-methyl or propargyl.

4. Use as claimed in claim 1, where the compound is in an amount between 0.05 mg/kg and about 1.0mg/kg of animal body weight.

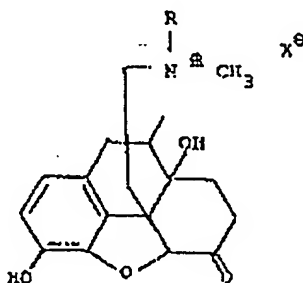
20 5. Use as claimed in claim 1, as an entercally  
administered compound;

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5. Use as claimed in claim 1, as parenterally administered compound.
7. Use as claimed in claim 6, as an injectably administered compound.
8. Use as claimed in claim 1, prior to the administration of the narcotic analgesic.
9. Use as claimed in claim 1, up to about two hours prior to the administration of the narcotic analgesic.
10. Use as claimed in claim 1, concurrently with the administration of the narcotic analgesic.
11. Use of methylnaltrexone to prevent or relieve nausea and emesis associated with the use of a narcotic analgesic in war-blooded animals.
12. Use as claimed in claim 11 in an amount of between 0.05 mg/kg of animal body weight and about 1.0 mg/kg of animal body weight simultaneously with or up to about two hours prior to the time of administration of the narcotic analgesic.
13. Use as claimed in claim 12, as a parenterally administered compound.

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14. A pharmaceutical composition for preventing or relieving nausea and emesis comprising a narcotic analgesic in combination with at least one quaternary derivative of  
 5 noroxymorphone:



wherein

R is allyl or a related radical; and

X is the anion of an acid;

- and wherein the quaternary derivative of noroxymorphone is  
 10 present in an amount effective to prevent or relieve nausea induced by the narcotic analgesic.

15. A pharmaceutical composition as claimed in claim 12 in which R is chloroallyl, cyclopropyl-methyl or propargyl.

16. A composition as claimed in claim 12 in which X is a  
 15 chloride, bromide, iodide or methanesulfate anion.

17. A composition according to claim 14, wherein the quaternary derivative of noroxymorphone is present in a unit dose of between about 0.05 mg and about 1.0 mg for each 1 mg of morphine.

- 20 18. A composition as claimed in claim 14, wherein the narcotic analgesic is morphine.

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19. A composition as claimed in claim 14, wherein the quaternary derivative of nicosymorphane is methylnaltrexone.



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QUATERNARY DERIVATIVE OF NOROXYMORPHINE  
WHICH RELIEVE NAUSEA AND EMESIS

ABSTRACT OF THE DISCLOSURE

Quaternary derivatives of noroxymorphone are used to prevent or relieve nausea and emesis associated with the use of narcotic analgesics without interfering with the analgesic activity of the drugs. A particularly preferred compound is methylbaltrexone. The compound is administered in a concentration between 0.05 mg/kg and 1.0 mg/kg prior to or concurrently with the administration of the narcotic analgesic.

**SUBSTITUTE**  
**REMPLACEMENT**

**SECTION is not Present**

***Cette Section est Absente***